

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)

Role of polymers in improving the results of stenting in coronary arteries

Tao Peng*, Paul Gibula†, Kang-de Yao† and Mattheus F.A. Goosen†

*Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A4; †Department of Chemical Engineering, Queen's University, Kingston, Canada K7L 3N6; ‡Department of Materials Science and Engineering, Tianjin University, Tianjin, People's Republic of China 300072

This article is a review of recent developments of polymer-related stents mainly employed in the coronary arteries, including polymer-coated stents, biostable stents and biodegradable stents. Polymer paving is covered as well. The problems with the stents currently investigated and the development of new stents are discussed.

Keywords: Polymeric stenting, intracoronary stents, metallic stents, polymer paving

Received 13 December 1994; accepted 8 June 1995

Percutaneous transluminal coronary angioplasty (PTCA) has been widely used for the treatment of coronary artery diseases¹. Despite continued improvement in equipment and the technical aspects of this procedure, abrupt or chronic closure and restenosis remain major limitations of PTCA^{2,3}. In order to improve PTCA, several methods are commonly applied such as prolonged inflation with perfusion balloons, use of larger diameter balloons, directional atherectomy, coronary artery bypass surgery or insertion of stents⁴. Pharmacological therapy has also been employed⁵.

Coronary stents have been used as a mechanical means to overcome the major limitations of balloon angioplasty⁶. The principle for intracoronary stenting is based on the scaffolding effects of the device, allowing the intimal and medial flaps to be tacked up, thus providing a smooth vessel lumen contour^{7,8}.

METALLIC STENTS AND RELATED PROBLEMS

Since Sigwart *et al.*⁹ reported the first implantation of a self-expandable, stainless steel stent in human coronary arteries, various intracoronary stents have been tested in an attempt to prevent occlusion and restenosis after angioplasty. Most of these stents are made of metals with a variety of designs which differ significantly in their geometry, composition and implant methods^{10,11}. Table 1 lists the characteristics of some intracoronary metallic stents commonly used.

Early experience with some of the metallic stents suggests that intracoronary stenting is effective in preventing or minimizing complications after angioplasty^{4,12-15}, especially as emergency bail-out

devices for acute arterial occlusion¹⁶. The great majority of clinical trials have been done with the Palmaz stent. The primary success rate is above 90%¹⁷.

Despite the high initial success rate, early and late complications such as thrombotic closure and restenosis have been reported with all current metallic stent devices^{14,18,19}. Clinical experience with Wallstents shows a poor late result (occlusion or significant restenosis at 6 months) in 38-56% of patients²⁰. Results from uncontrolled clinical studies with coronary stents made of stainless steel indicated that these devices were prone to occlusion due to (sub)acute thrombosis^{9,20,21}. Recently, it was reported in both the Benestent study²² and the stress restenosis study (STRESS)²³ that coronary stenting demonstrated efficiency in restenosis reduction; however, several caveats on the results reported from the Benestent and STRESS trials have been discussed which suggested some reduction in the benefit²⁴. The experience with tantalum coronary stents after implantation in patients indicated no significant advantage of tantalum over stainless steel stents²⁵. Furthermore, some stents are difficult to handle. For example, Nitinol stents tend to expand prematurely while in the guiding catheter²⁶. It was reported that when metallic stents were overexpanded in porcine coronary vessels, a reproducible model of neointimal proliferation that is morphologically identical to human restenosis is observed²⁷.

Theoretically, there are some concerns about metallic stents. It is known that net electrical charge or potential of the surface is a critical factor determining the biological response of a metal in contact with blood²⁸. The surfaces of most metals are electropositively charged and therefore are thrombogenic because blood elements are negatively charged²⁹. Tantalum stents have a negative net surface potential after complete surface cleaning but turn electropositive after several hours of exposure to air or electrolytic solutions³⁰.

Correspondence to Dr M.F.A. Goosen, College of Agriculture, Sultan Qaboos University, PO Box 34 Al-Khod, Postal Code 123, Muscat, Sultanate of Oman.

Table 1 Properties of some intracoronary metallic stents

Name of the stent	Composition	Geometry	Working mechanism
Gianturco-Roubin	Stainless steel	Resembling the binding of a spiral notebook	Balloon-expanding
Palmaz-Schatz	Stainless steel	Tube bearing staggered rows of rectangular slots	Balloon-expanding
Strecker	Tantalum	Tubular mesh	Balloon-expanding
Wiktor	Tantalum	Helical pattern	Balloon-expanding
Nitinol	Titanium-nickel	Coiled tube	Self-expanding
Wallstent	Stainless steel	Wire mesh	Self-expanding
Z stent	Stainless steel	Cylinder shape	Self-expanding

Another surface property that affects metal reactivity with blood is free surface energy which is related to critical surface tension. Most metals have a high critical surface tension resulting in high thrombogenicity³⁰. In addition, as a metal stent remains in the body indefinitely, it may interfere with future clinical procedures³¹. Moreover, the stent becomes a permanent foreign body with potentially important interactions due to the type of metal, electrostatic charges and possible physical irritation from individual filaments leading to long-term effects¹⁸. The mismatch in mechanical behaviour between the stent and vessel wall can result in excessive intimal proliferation and a high risk of thrombosis^{17,30}. Continuous barotrauma and localized areas of necrosis may be induced by the long-term expandable forces generated by the stent attempting to return it to its unconstrained size. Individual allergy is also a concern to those who are hypersensitive to the metals that make up the device¹⁸. Permanent implantation could also generate problems due to mechanical stability and corrosion, eventually resulting in the perforation of the vessel wall³².

CURRENT STATE OF DEVELOPMENT OF NOVEL STENTS

The problems with metallic stents have encouraged significant efforts to develop new stents to produce a non-thrombogenic stent site and obviate the problems of restenosis and neointimal hyperplasia. The developments of the new designs are related to their composition and fundamental geometry (tube, mesh or single wire). In addition, various subtle changes such as thickness of filaments, alloy composition ratio, surface roughness and biocompatible or therapeutic coatings have been investigated as well. For example, research has been done to coat the metal surface of the stent with genetically engineered endothelial cells to decrease the thrombogenicity of the stent³³. Polymer coatings were also employed to render the stent surface less thrombogenic³⁴. The design of the surface geometry of the stents may affect the stenosis rate in the stented arterial segments. It was reported that a coiled stent made of titanium-nickel wire with gaps between the individual coils showed significantly lower stenosis rate than those without gaps²⁶.

Another effort is the development of the temporary metallic stent³⁵⁻³⁷. The goal of temporary stenting is to mitigate acute occlusion by allowing flow through the lumen and then removing the stent to avoid long-term

complications. Theoretically, these devices may be superior to permanent stents when it is temporarily needed to split the coronary artery after significant dissections or haemodynamically important elastic recoil. However, the complexity of these stents and the added trauma involved in the retrieval process may offset their advantages.

On the other hand, attention has been drawn to stents made of new materials such as polymers, either biostable or biodegradable, which would offer some advantages over metallic stents, but could also act as a carrier for controlled release of drugs to mitigate the tissue response to the foreign material³⁸. In addition, the development of new pharmacological interventions may prevent thrombosis without the need for aggressive anticoagulation after stenting^{39,40}. Research on the basic biology and materials science of stents should lead to further advances as well.

This paper will provide a review on polymeric stenting to show the role of polymers in the development of intracoronary stenting. Polymer-coated stents, biostable polymer stents and biodegradable stents will be covered in the discussion.

POLYMER-COATED STENTS

Some efforts have been made to coat metallic stents with polymers using different methods to diminish their thrombogenic properties. A Nylon[®] mesh, Gianturco self-expanding metallic stent was developed by Yoshioka *et al.*⁴¹ for an arterial endovascular graft. The Gianturco stent was covered with an expandable Nylon mesh. The resultant device was delivered via transcatheter techniques forming a cylinder that created a tight fit between the stent and the vessel wall after implantation. The Nylon acted as a support for neointimal encasement which formed a new vascular lumen. Furthermore, since the weave of the Nylon material used was relatively loose, blood was able to flow through the mesh into the side branches bridged by the material. One disadvantage of the device was that it required a 12-French catheter for introduction due to the stent construction and the elasticity and thickness of the Nylon material. This would cause difficulty on deployment of the stent in coronary arteries because of its small calibre. Roeren *et al.*⁴² reported a Palmaz-silicone stent which is coated with a medical-grade silicone polymer. The coated stents were percutaneously placed into the aorta of rabbits and monitored by angiography. It was shown that all implanted silicone-coated stents were biocompatible.

No in
were
occlus

As
polyu
stents.
polyu
ballo
coron
was s
acute
model

Drug
et al
polyu
coval
invest
with
reveal
throm
impla
accum
patent

Sch
stent
select
which
readil
synthe
proper
apply
site
respon
or thro

By
soluti
forme
fibrin
stent
assess
polyu
occlus
with
polyu
stents



Figure
sleeve
(Repr

No inflammatory, foreign-body or fibrotic reactions were observed. Intimal hyperplasia, leading to occlusion, was still a potential problem.

As a widely used cardiovascular biomaterial, polyurethane was considered for coating metallic stents. De Scheerder *et al.*⁴³ studied amphiphilic polyurethane-coated, stainless steel, slotted tube, balloon expandable stents implanted in porcine coronary arteries compared with non-coated stents. It was shown that the polyurethane coating decreased acute thrombotic occlusion in the porcine coronary model.

Drug-eluting polymer coating was reported by Sheth *et al.*⁴⁴. Bare metal Nitinol stents coated by polyurethane-polyethylene oxide copolymer with covalently bound heparin were developed and investigated in the carotid arteries in a comparison with uncoated stents. The results with all stents revealed a high frequency of occlusive and subacute thrombosis in the rabbit carotid model after implantation for 96 h. However, the coated stents accumulated less thrombus and tended to have better patency in a rabbit model of subacute thrombosis.

Schwartz and co-workers^{38,45} developed a tantalum stent coated with a natural polymer, fibrin. Fibrin was selected as a candidate, since it is a native polymer which deposits naturally at sites of vessel injury, is readily available and bioabsorbable, and can be synthesized with excellent elastomeric mechanical properties. The stents coated with fibrin film would apply a controlled layer of preformed thrombus at the site of damaged vessel to 'fool' the body's own response to this event and thereby limit its reparative or thrombotic reaction⁴⁶.

By dripping fibrinogen solution and thrombin solution directly onto a Wiktor stent, a fibrin layer formed on the stent. Subsequent polymerization of the fibrin leads to a fibrin mass completely encasing the stent (Figure 1). The stents covered by fibrin film were assessed in a porcine coronary model in contrast with polyurethane-coated stents. It was shown that vessel occlusion and a foreign-body inflammatory response with multinucleated giant cells were observed with polyurethane-coated stents. However, fibrin-coated stents seemed promising for modification of the local

response to arterial injury and reduced restenosis rates. Variations in ionic strength, pH, fibrinogen and thrombin concentrations affected the final fibrinogen roughness. In addition to coating stents, the fibrin matrix may be used to incorporate microcapsules for local drug-controlled release. There were several problems with the stent that need to be addressed, including donor infection, specific formulation, immunological response and optimal delivery method.

A drug-eluting biodegradable polymeric coating has also been reported⁴⁷. A tantalum wire coil stent coated with a 20–25 µm layer of dexamethasone suspended within a binder of a biodegradable polymer, poly-L-lactic acid ($M_w = 321\,000$), was evaluated in the porcine coronary injury model. It was demonstrated that the tissue responses to coated and uncoated stents are identical. The polymer did not evoke an inflammatory reaction. Dexamethasone did not exhibit limitation of neointimal proliferation but the coated drug-eluting stent proved to be an effective and well-tolerated means of intravascular sustained drug delivery.

Incorporation of drugs into polymer coating (i.e. drug-eluting polymer coatings) may be useful to improve polymer-coated stents. However, the thin polymer coating may only be able to carry a limited amount of drug thus making it difficult to maintain high local drug concentration for an extended period of time. The efficiency of this local drug delivery will also be affected by permeability of drugs into the vessel wall. The kinetics, distribution and bioactivity of forskolin, an antiplatelet and vasodilator drug, released from a polyurethane-coated removable metallic stent was assessed⁴⁸. It was concluded that the polymer-coated stent can deliver forskolin to the arterial wall in high concentration relative to the blood or other tissues. Local tissue and blood kinetics can be modelled as a simple diffusion process. Tissue forskolin levels are proportional to the drug remaining on the stent and are dependent on maintaining stent-to-tissue drug gradients. The delivered drug is biologically active possessing vasodilating and antiplatelet function.

POLYMER STENTS

In addition to polymer-coated metallic stents, stents completely made of polymeric materials are being tested as an alternative to metal stents. In fact, polymers have been widely used in cardiovascular devices as listed in Table 2.

Although it is predicted that polymer stents are potentially useful^{8,31,48,50,54,55}, the study of intracoronary polymer stents has not gained very widespread popularity. This review introduces polymer stents to show their current status.

There are several reasons to fabricate a stent composed of a polymer. First, significant progress has been achieved in increasing the level of blood compatibility of polymers. Second, by selecting suitable monomer units, polymerization procedures and processing techniques, the properties (e.g. surface characteristics and mechanical strength) of the stents

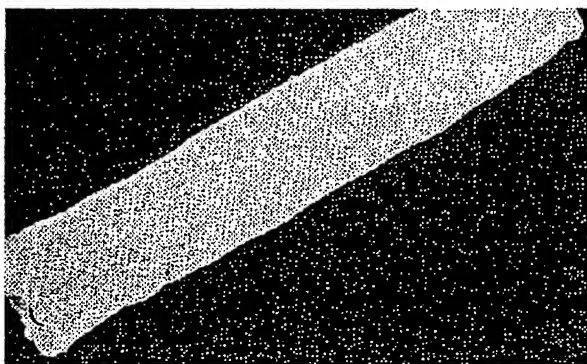


Figure 1 Fibrin-coated tantalum metal wire stent. Fibrin sleeve configured as a thin, balloon-expandable cylinder³⁸. (Reproduced with permission of the Publisher.)

Table 2 Polymers for cardiovascular devices

Polymers	Applications	Ref.
Epoxy resin, polysulphone, polycarbonate	Heart valves, ventricle housing materials	49
Polyethylene	Vascular grafts, PTCA* balloons, vascular catheter	50
Polyethylene terephthalate (Dacron [®])	Arterial grafts	49
Polytetrafluoroethylene (Teflon [®])	Arterial grafts, blood gas exchange device	49
Polysiloxane, polypropylene	Blood gas exchange device	49
Polyurethane	Angioplasty, catheters, pacemaker interfaces and leads, vascular grafts	51
Silicone rubbers	Blood pump, cardiac pacemaker leads, heart valve poppets	52
Polycaprolactone or poly(caprolactone-co-lactide)	Vascular prostheses	53

* PTCA = percutaneous transluminal coronary angioplasty.

can be controlled in an attempt to get smooth synthetic polymer surfaces. This would significantly reduce the activation of blood coagulation⁵⁶. It would also result in a better fit of the stent against the arterial wall which would decrease subsequent neointimal hyperplasia caused by acute and chronic vessel injury⁵⁷. Third, polymer stents can incorporate or bind drugs for later local controlled delivery at the target site that would inhibit thrombus formation and neointimal proliferation⁵⁸. It has been estimated that a polymer stent can deliver a drug dose to the target site in the coronary artery that is 10 times higher than systemic administration⁴⁶. Local administration of various drugs including urokinase⁵⁸, heparin^{59, 60}, taxol⁶¹, hirudin⁶² and peptide⁶³ are being investigated to prevent thrombosis and restenosis.

Polymer stents composed of plastic materials like Dacron[®] and Teflon[®] have been implanted successfully in biliary and urinary tracts^{14, 64}. Straight polyethylene stents were also tested for treatment of distal malignant biliary obstruction⁶⁵. Teflon stents have also been used for lymphovenous anastomosis⁶⁶. On the other hand, bioresorbable urethral and ureteral stents based on biodegradable polymers such as poly(L-lactide) and its copolymers were also attractive due to their good biocompatibilities and biodegradabilities^{67, 68}.

With this information in mind, it is possible to consider a polymer stent which can overcome drawbacks of presently available stents. Several issues are important, including performance requirements, device design, material selection, blood and tissue compatibility, and *in vivo* performance, which have been discussed by Zdrahala³². Material composition and stent design may be the most important ones. There has been much discussion concerning the material and design of stents⁶⁹. The material of the stent strongly affects the mechanical properties and

the propensity to thrombosis and to endothelialization^{17, 19}. Stents with appropriate flexibility would improve the ability to deliver them in tortuous arteries and reduce the risk of damage to the arterial wall⁷⁰. Improvements in stent design may also contribute to a reduction in thrombotic events⁵⁴. In addition, because of relatively weak strength, greater bulk may be needed for polymer stents than metallic stents. Single coil polymer stents may not provide enough support against the vessel wall.

According to the stability of the material under physiological conditions, polymer stents can be further divided into biostable polymer stents and biodegradable stents.

Biostable polymer stents

The principle of this stent design is to maintain luminal integrity of the coronary vessel, in a similar manner to that achieved with current metallic stents, and remain biologically permanent following coverage with endothelium.

A flexible, self-expanding polyethylene terephthalate (PET) stent and a delivery system for implantation in porcine coronary arteries were developed and tested by Murphy and co-workers^{55, 71, 72}. The polymer stent was deployed in the coronary arteries of 11 Yucatan swine by withdrawal of an outer polyethylene delivery sheath, thus allowing the PET stent to self-expand to a preformed configuration (Figure 2). The study showed that percutaneous deployment of polymeric stents in the coronary arteries was technically feasible and PET possesses the necessary mechanical properties for use as a stent. However, the PET stent led to an intense inflammatory and neointimal proliferative response that resulted in vessel occlusion. Histological examination of the stented site indicated no evidence that the dissection of the vessel wall had occurred at the time of initial stent deployment. The research may be useful for the selection of material for use as an intravascular device. The authors stated that though polymer stents have major potential advantages over metallic stents and can be configured in an appropriate design for intracoronary delivery, significant biomaterial problems, such as neointimal proliferation, need to be addressed before clinical tests can begin.

Van der Giessen and co-workers^{73, 74} studied a self-expanding braided mesh stent also made of PET for percutaneous coronary artery implantation. The mechanical features of the polymer stent were

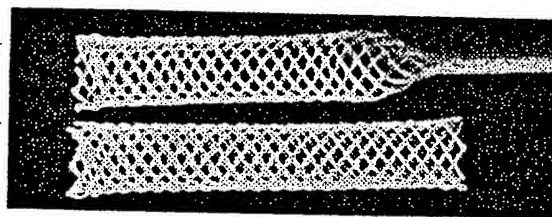


Figure 2 Photograph of a self-expanding biostable polyethylene terephthalate stent. The stent was mounted within a delivery sheath (top). After the delivery catheter was removed, the expanded meshwork stent (bottom) was in place⁵⁵. (Reproduced with permission of the Publisher.)

inves
imagi
angio
after
pigs.
imple
press
expar
like t
braidi
polyn
initia
of the
settin
acute
and
hyste
mour
place
60%
asses
of the
locate
syster
paten

Biodi

Biode
remai
the ve
subst
functi
can
proce
degra
degre
The c
time
profil
adjust
Agr
bioab
acid)
were
methc
stents
braidi
mesh
were
fixed
were
of me
the m
can w
and m
the s
surpa
margi
polyn
press
decre
ratio
polym

investigated by *in vitro* measurements and the *in vivo* imaging of the stent was assessed by autopsy analyses, angiography and intravascular ultrasound examination after the implantation of the stents in the arteries of pigs. Heparin was administered only during the implantation procedure. It was shown that the radial pressure delivered by this device was similar to a self-expanding, stainless steel stent. However, hysteresis-like behaviour was noticed and attributed partly to the braided construction and partly to a feature of the polymer material itself. This behaviour would result in initial loss of the radial pressure and a slower build-up of the pressure. It could consequently lead to a softer setting of the stent against the vessel wall, reducing acute vessel wall damage and neointimal proliferation and restenosis. On the other hand, because of its hysteresis-like behaviour, the polymer stent should be mounted on the delivery system just before the placement procedure, with an unconstrained diameter 60% larger than that of the target vessel. *In vivo* assessment revealed that after 4 wk implantation, one of the stents was occluded and two other stents were located incorrectly due to failure of the delivery system. Five of six correctly implanted stents were patent.

Biodegradable polymer stents

Biodegradable polymer stents have the potential to remain *in situ* for a predicted period of time keeping the vessel wall patent and then degrading to non-toxic substances. Therefore, after completion of their functions and resorption of the stents, the vessel wall can preserve its normal function and surgical procedures to remove the stent are avoided. The degradation rate of the stent can be controlled by the degree of polymerization and processing methods^{67,75}. The change in mechanical properties of the stent over time would be affected by the degradation. The release profiles of drugs from a biodegradable stent can also be adjusted by the degradation behaviour⁷⁵.

Agrawal and co-workers^{31,76} reported a bioabsorbable intravascular stent made of poly(L-lactic acid) (PLLA). The mechanical properties of the stent were tested as a function of thermal treatment methods, stent diameter and filament draw ratio. The stents were fabricated from monofilaments of PLLA by braiding eight monofilaments into an open tubular mesh using an over-under type of weave. The stents were then annealed at 140°C for 0.25 h with their ends fixed. Finally, at the free ends, adjacent monofilaments were welded together using a polymer solution. Tests of mechanical properties of the stents indicated that the maximum hydrostatic pressure that the PLLA stent can withstand decreases with increasing stent diameter and monofilament draw ratio. The collapse pressure of the stents with the 6:1 draw ratio monofilaments surpassed the target pressure of 300 mmHg by a wide margin³¹. The deformation characteristics of the polymeric stents at pressures lower than their collapse pressures showed that the effective elastic modulus decreased with increasing stent diameter and draw ratio. However, unlike metallic stents, the strength of a polymeric stent does not exhibit a linear relationship

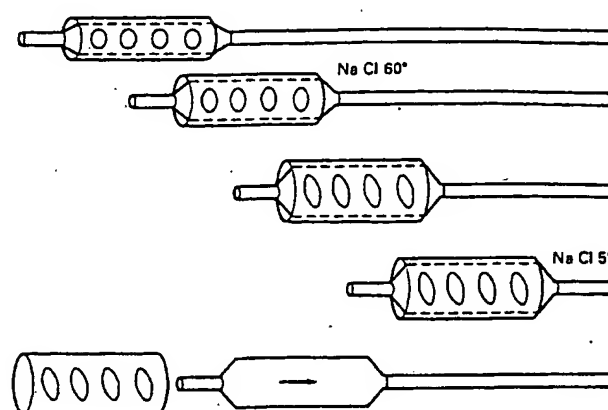


Figure 3 Heat-labile expandable polycaprolactone stent which can be expanded at 60°C using a hot balloon catheter⁷⁸. (Reproduced with permission of the Publisher.)

with initial stent diameter³¹. The *in vivo* test was done by placing the stent in femoral arteries of dogs. It was indicated that this bioabsorbable stent was deployable, became endothelialized, remained patent and did not induce a significant inflammatory and thrombotic occlusion⁷⁶. Based on its mechanical properties and *in vivo* assessment, it was concluded that PLLA is a very strong candidate for use as a material for bioabsorbable polymeric stents^{31,76,77}.

Another promising biodegradable polymer used for stents is polycaprolactone. Polycaprolactone was employed to make a heat-labile balloon-expandable plastic stent⁷⁸. Since polycaprolactone is a therm-elastomer which is soft from 52 to 70°C, the stent can be shaped to suit the vessel wall, the bile ducts or bronchial tree by a hot balloon technique or other heating methods. For example, the balloon can be heated simply by means of a warm NaCl solution (Figure 3), electric matter in the balloon itself or microwaves. The stent may even be heated directly to the necessary temperature leading to the expansion of the stent so that it can be embedded in the vessel wall to prevent migration and provide sufficient support to overcome the forces of vascular spasm. This stent may be used to reconstruct intraluminal vessels, the bile ducts and even the bronchi.

Recently, a patent on multilayered biodegradable stents was claimed⁷⁹. The stent is made of various polymers such as PLLA, polyglycolic acid, polycaprolactone, polyorthoesters or polyanhydrides. The unique feature of the device is that one layer addresses the structural requirements of the stent and additional layers control the release of different drugs such as heparin or angiopeptin at predictable rates. The different layers are laminated to one another by using heat or solvents. The laminated construction allows combination in a single stent of a plurality of different drug-containing materials. By appropriate configuration of the layers, drug release characteristics can be adjusted. Furthermore, different layers of the anatomy can be targeted for treatment using different drugs. For example, the layer associated with the exterior surface of the stent can control drugs such as angiopeptin, methotrexate and heparin to be released

into the vessel wall to discourage restenosis. The layer associated only with the interior surface of the stent would cause drugs like prostacyclin to be released into the lumen to prevent coagulation. In such a case, the structural layer will be laminated between these two drug-containing layers. The device can be fabricated with proper mechanical properties (strength and flexibility). The major concern with this type of stent may be that it is difficult to deploy and fix within the vessel wall.

In order to assess the intraarterial compatibility of some biodegradable polymers including polyglycolic/poly(lactic acid), polycaprolactone and poly(hydroxybutyrate valerate), the polymer films were cast longitudinally over 90° of the circumferential surface of coil wire stents which were then implanted in porcine coronary arteries⁸⁰. The vessel wall adjacent to the polymer was compared with that in contact with uncoated stent wire. Histopathology after 30 d post-implantation revealed that in contrast to the control, polymer strips resulted in extensive fibromuscular proliferation, mononuclear and eosinophilic cell infiltration, multinucleated giant cell formation and medial necrosis leading to eccentric stenoses. There is a need to combine polymer stents with drug delivery systems to improve tissue response.

Biodegradable copolymer stents carrying drugs and ligand-regulating cell functions

As mentioned above, polymer stents have the potential to act as drug delivery systems. Polymeric materials, especially biodegradable polymers, have been widely utilized for controlled release of drugs. Therefore, it is possible to design a biodegradable polymer stent not only offering a physical barrier to the vessel wall, but also presenting a pharmacological approach in the prevention of thrombosis and intimal proliferation.

Although polycaprolactone is promising for stent applications, it would be difficult to covalently immobilize peptide or drugs inhibiting foreign-body response because no functional groups exist on polycaprolactone. To achieve functional group addition, a novel biodegradable copolymer could be synthesized by copolymerization of a monomer containing protected functional groups (i.e. cyclic dimer of lactic acid and protected lysine) with caprolactone⁸¹. Biologically active compounds such as RGD peptide, a cyclic integrin antagonist peptide, can be chemically attached onto pendant amino groups

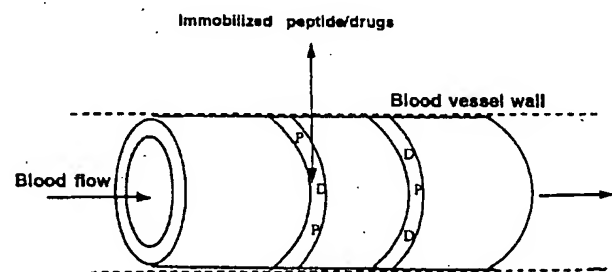


Figure 4 Schematic of a bioabsorbable copolymer stent carrying drugs and peptide-regulating cell functions. (P, peptide; D, drugs.)

from lysine units of a copolymer without significant reduction of biological activity^{82,83}. Localized delivery of the peptide can reduce neointimal hyperplasia⁸⁴. In addition, anticoagulant molecules (such as heparin) will be bound to the stent through the functional groups of the material⁸⁵. The peptide and drug could be delivered with the preprogrammed degradation of the stent to maintain high local drug concentration for a desired period of time. It is expected that a stent made of this material may be implanted to maintain position using the same technique as the polycaprolactone stent reported by Beck⁷⁸. The stent contains drugs and cell function regulating ligands that prevent thrombosis and intimal hyperplasia. Figure 4 shows the hypothesis of this device.

LIMITATIONS OF POLYMER STENTING

One concern with polymeric coatings is that the coating surfaces may be damaged by the balloon catheter during deployment. Questions still remain about the effects of stents on endothelialization and long-term patency even though a polymer coating can reduce the thrombogenicity of metallic stents³⁰.

The strength of polymers is intrinsically lower than that of metals or alloys, which means that stents made of polymers must have greater bulk to approximate the mechanical performance required for a metallic stent⁵⁰. For biodegradable stents, it is possible that by the time the stent disappears from the treated site, the atrophic changes that invariably occur when the musculoelastic elements of the arterial wall are not used may lead to aneurysmal dilatation³⁰. The bulk limitation of polymer stents may be increased in small vessels, while the risk of aneurysmal formation and rupture would be of concern in large vessels. The compromise can be found in polymer-coated metallic stents where the metal provides optimal mechanical strength while the polymer improves its surface properties.

Lack of radio-opacity is another limitation in the clinical application of polymer stents. It is difficult to deploy the stent easily and precisely without fluoroscopic visualization. By using intravascular ultrasound technique, the problem may be solved⁷⁴.

IDEAL STENTS

Experience with various stents leads to the required attributes of an ideal stent. While the ideal stent does not exist and all of the presently investigated stents have advantages and disadvantages, the essential properties of such a design are listed in Table 3; this helps to understand the relative merits of the devices and the improvements needed in each. First, as a cardiovascular implant, the stent should be biocompatible, especially blood compatible, i.e. should not elicit a foreign-body reaction within a human vessel wall. This is dependent on the stent's composition and surface characteristics of the stent (e.g. surface chemistry, surface energy and texture, etc.). Next, the biomechanical behaviour and design of the stent also have important effects on the host's

Polymer

Table 3

Aspect

Biocom

Mechan
propert

Safety

Compa
deploy

PTCA =

respor
induct
abrupt
and th
wall s
and th
stent r
the cu
to the
diameter
stable
migrat
proper
and ra

POLY

Polym
Slepi
intrac
were a
and in
polym
wall
render
thromb
mitoge
would
layer
stiffne
posse
suppo
thromb
the m
the m
vessel

CONC

Intrac
techni

Table 3 Characteristics of an Ideal stent

Aspects	Properties	Refs.
Biocompatibility	Non-thrombogenicity, endothelialization, no intimal proliferation and biologically inert	17, 19, 54
Mechanical properties	Adequate elasticity and reliable expandability, proper radial strength and expansion ratio, flexible and trackable enough to be deployed	17, 19, 54
Safety	Thin enough not to disrupt the smooth intimal lining; calibre maintained for long-term patency	17, 54
Compatible deployment	Radio-opacity, deployable on a very low profile catheter system; deliverable with minor adaptations of present PTCA* techniques; precise delivery to the target site	17, 19

*PTCA = percutaneous transluminal coronary angioplasty.

response. For example, the inflexibility of stents may induce arterial kinking at transition zones resulting in abrupt closure. An unsuitable stent/artery size ratio and the expandable force of the stent against the vessel wall seems to stimulate excessive intimal proliferation and thus result in late restenosis¹⁷. Finally, the ideal stent must be easily and precisely positioned through the curves of the guiding catheter and tortuous artery to the target site. Then it can be expanded to a diameter suitable for the size of the artery to offer a stable support against the vessel wall without risk of migration. This will depend on the mechanical properties (e.g. flexibility and elasticity), stent design and radio-opacity, etc.

POLYMER PAVING

Polymeric endoluminal paving was developed by Slepian and co-workers⁸⁶⁻⁹⁰ as an alternative to intracoronary stenting. Biodegradable polymer layers were applied to the vessel wall via a catheter technique and *in situ* photo-thermal paving. The thin endoluminal polymeric film can conform to the shape of the vessel wall on a cellular length scale⁸⁹. This technique rendered damaged vessel surfaces essentially non-thrombogenic and provided a diffusional barrier to mitogenic factors derived from the plasma, which would prevent thrombosis and restenosis. The polymer layer can be prepared, with adequate structural stiffness, incorporating drugs to result in a device possessing the capability of providing a physical support to keep the vessel wall patent while preventing thrombosis and restenosis. More research is needed on the mechanism of delivery of polymer to the target site, the method of curing of the polymer without causing vessel damage and the occlusion of side branches⁵⁰.

CONCLUSIONS

Intracoronary stenting provides a new interventional technique to prevent late restenosis and closure

following balloon angioplasty. However, high rates of thrombosis restrict stent applications. The problem might be solved by further improvements in materials from which the stent is constructed and in its design, which will require joint efforts by interventional cardiologists, pathologists, biochemists, material scientists and engineers. Clearly, the material of the stent influences the mechanical properties and also the risk of thrombosis and intimal hyperplasia.

Polymeric stenting provides a possibility for combining physical treatment with pharmaceutical therapy perhaps leading to new generation of stents. The general principle of all intravascular stents is to oppose the elastic recoil of vascular stenoses and provide internal support. Therefore, the mechanical and viscoelastic properties of stents must be tested at first, especially for polymer stents which are intrinsically weaker than metallic stents. Drugs or peptide contained within polymers can be in a non-chemically bonded configuration or chemically bonded to the polymer side chains. It is expected that chemical incorporation of drugs or peptide may further enhance the extended release compared with physical entrapment. In particular, biodegradable polymers can be used for controlled drug delivery. If the problems of thrombosis and restenosis could be overcome by polymeric stenting, this new method would gain more attention.

Initial experiences with polymer stents in different animal models have given variable results. The results with PET stents reported by van der Giessen *et al.*⁷³ are considerably better than those reported by Murphy *et al.*⁷². Two factors were considered for the difference⁷³: (a) the PET stents deployed by van der Giessen *et al.* have a larger unconstrained diameter (5.3 mm) compared with the stents designed by Murphy *et al.* with a diameter of 3 mm, which may have resulted in the 100% occlusion rate due to thrombosis; (b) the compositions of PET were not identical.

Severe tissue responses were identified with some biodegradable polymers in a porcine model⁸⁰, in contrast to indications of good blood compatibility obtained for biodegradable polymers such as PLLA⁷⁷. More trials and development of materials and techniques are necessary to bring new devices to clinical study and to confirm whether polymeric stents are of passing interest only.

Polymer-coated metallic stents may be the first used in widespread clinical trials. These stents have radio-opacity and good radial strength. The polymer coating will allow modification of the stent surface and incorporation with drugs to reduce thrombosis and intimal hyperplasia.

Intravascular ultrasound has the potential for development of delivery systems that allow accurate delivery of polymer stents without the need for fluoroscopic visibility. In the future development of polymeric stents, biodegradable stents may be designed so as to incorporate time-release antiproliferative substances such as bioengineered growth factor inhibitors or to covalently immobilize cell function regulating peptides, to yield improved stent applications.

REFERENCES

- 1 Clark DA. *Coronary Angioplasty*. Wiley-Liss Inc., 1991.
- 2 Hearn JA, King SB, Douglas JS, Carlin SF, Lembo NJ, Ghazz IBM. Clinical and angiographic outcomes after coronary artery stenting for acute or threatened closure after percutaneous transluminal coronary angioplasty. *Circulation* 1993; 88: 2088-2096.
- 3 Waller BF, Orr CM, Pinkerton CA, Van Tassel JW, Pinto RP. Morphologic observations later after coronary balloon angioplasty: mechanisms of acute injury and relationship to restenosis. *Radiology* 1990; 174: 961-967.
- 4 Colombo A, Goldberg FSL, Almagor Y, Maiello L, Finci L. A novel stent deployment in the treatment of acute or threatened closure complicating balloon coronary angioplasty. *J Am Coll Cardiol* 1993; 20: 1887-1891.
- 5 Hanke H, Oberhoff M, Hanke S et al. Inhibition of cellular proliferation after experimental balloon angioplasty by low-molecular-weight heparin. *Circulation* 1992; 85: 1548-1556.
- 6 Savage PM, Fischman DL, Schatz RA et al. Long-term angiographic and clinical outcome after implantation of a balloon-expandable stent in the native coronary circulation. *J Am Coll Cardiol* 1994; 24: 1207-1212.
- 7 Alfonso F, Hernandez R, Goicoler J. Coronary stenting for acute coronary dissection after coronary angioplasty: implications of residual dissection. *J Am Coll Cardiol* 1994; 24: 989-995.
- 8 Becker GJ. Intravascular stents: general principles and status of lower-extremity arterial applications. *Circulation* 1991; 83: 1-122-1-136.
- 9 Sigwart U, Prel J, Mirkoritch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *New Engl J Med* 1987; 316: 701-706.
- 10 Schatz RA. A view of vascular stents. *Circulation* 1989; 79: 445-457.
- 11 Serruys PW, Beatt KJ, van der Giessen WJ. *Eur Heart J* 1989; 10: 774-782.
- 12 Geore BS, Voorhees WD, Roubin GS. Multicenter investigation of coronary stenting to treat acute or threatened closure after percutaneous transluminal coronary angioplasty: clinical and angiographic outcomes. *J Am Coll Cardiol* 1993; 135-143.
- 13 Kimura T, Nosaka H, Iwabuchi M, Nobuyoshi M. Serial angiographic follow-up after Palmaz-Schatz stent implantation: comparison with conventional balloon angioplasty. *J Am Coll Cardiol* 1993; 21: 1557-1563.
- 14 Bar FW, van Oppen J, de Swart H et al. Percutaneous implantation of a new intracoronary stent in pigs. *Am Heart J* 1991; 122: 1532-1541.
- 15 Fischman DL, Savage MP, Leon MB et al. Fate of lesion-related side branches after coronary artery stenting. *J Am Coll Cardiol* 1993; 22: 1641-1646.
- 16 Sigwart U, Urban P, Golf S. Emergency stenting for acute occlusion after coronary balloon angioplasty. *Circulation* 1988; 78: 1121-1127.
- 17 Yang XM, Manninen H, Matsi P, Soimakallio S. Percutaneous endovascular stenting: development, investigation and application. *Eur J Radiol* 1991; 13: 161-173.
- 18 Serruys PW, Strauss BH, van Beusekom M, van der Giessen WJ. Stenting of coronary arteries: has a modern Pandora's box been opened? *J Am Coll Cardiol* 1991; 17: 143B-154B.
- 19 Satler LF, Popma JJ, Mintz GS et al. New revascularization devices: update on coronary stents. *Prim Cardiol* 1993; 19: 18-30.
- 20 Serruys PW, Strauss BH, Beatt KT. Angiographic follow-up after placement of a self-expanding coronary artery stent. *N Engl J Med* 1991; 324: 13-17.
- 21 Garratt KN, Holmes DR. Early outcome after placement of metallic intracoronary stents: initial Mayo Clinic experience. *Mayo Clin Proc* 1991; 66: 268-275.
- 22 Serruys PW, Jaegere PD, Kiemeneij F et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *New Engl J Med* 1994; 331: 489-495.
- 23 Fischman DL, Leon MB, Baim DS et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *New Engl J Med* 1994; 331: 496-510.
- 24 Topol EJ. Caveats about elective coronary stenting. *New Engl J Med* 1994; 331: 539-541.
- 25 De Jaegere PP, Serruys DW, Bertrand ME, Wiktor stent implantation in patients with restenosis following balloon angioplasty of a native coronary artery. *Am J Cardiol* 1992; 69: 598-602.
- 26 Tominaga R, Kambic HE, Emoto H, Harasaki H, Sutton C, Hollman J. Effects of design geometry of intravascular endoprostheses on stenosis rate in normal rabbits. *Am Heart J* 1992; 123: 21.
- 27 Schwartz RS, Murphy JC, Edwards WD. Restenosis after balloon angioplasty: a practical proliferative model in porcine coronary arteries. *Circulation* 1990; 82: 2190-2200.
- 28 De Palma VA, Bauerre FJW, Gett VL, Furuse A. Investigation of three-surface properties of several metals and their relation to blood compatibility. *J Biomed Mater Res Symp* 1972; 3: 37-75.
- 29 Riveiro PA, Gallo R, Antonius J et al. A new expandable intracoronary tantalum (Strecker) stent: early experimental results and follow-up to twelve months. *Am Heart J* 1993; 125: 501-510.
- 30 Palmax JC. Intravascular stents: tissue-stent interactions and design considerations. *Am J Radiol* 1993; 160: 613-618.
- 31 Agrawal CM, Haas KF, Leopold DA, Clark HG. Evaluation of poly(L-lactic acid) as material for intravascular polymeric stents. *Biomaterials* 1992; 13: 176-182.
- 32 Zdrahala RJ. Absorbable poly(alpha ester) materials for temporary endovascular stenting in balloon angioplasty (PTCA). *The 16th Annual Meeting of the Society of Biomaterials* 20-23 May 1990: 155.
- 33 Dichek DA, Neville RF, Zwiebel JA, Freeman SM, Leon MB, Anderson WF. Seeding of intravascular stents with genetically engineered endothelial cells. *Circulation* 1989; 80: 1347-1353.
- 34 van der Giessen WJ, van Beusekom HMN, van Howten CD, van Woerkens LJ, Verdouin PD, Serruys PW. Coronary stenting with polymer coated and uncoated self-expanding endoprostheses in pigs. *Cor Art Dis* 1992; 3: 631-640.
- 35 Schlarsky-Goldberg RD, LeVeen RF, Hillstead RA, Lope C. Temporary vascular stenting (abstr.). *Radiology* 1990; 177: 299.
- 36 Khorsandi MJ, Eigler NL, Hess RL, Lallister JP, Forrester JS, Litvack F. Implantation and recovery of balloon delivered removable stent (abstr.). *J Am Coll Cardiol* 1992; 19: 218A.
- 37 Gaspard PE, Didier BP, Delsanti GL. The temporary stent catheter: a non-operative treatment for acute occlusion during coronary angioplasty (abstr.). *J Am Coll Cardiol* 1991; 15: 118A.
- 38 Holmes DR, Camrud AR, Jorgenson MA, Edwards WD.

- Schwartz RS. Polymeric stenting in the porcine coronary artery model: differential outcome of exogenous fibrin sleeves versus polyurethane-coated stents. *J Am Coll Cardiol* 1994; 24: 525-531.
- 39 Blengino S, Maielo L, Hall P, Nakamura S, Giovanni M, Colombo A. Randomized trial of coronary stent implantation without anticoagulation aspirin vs. ticlopidine. *Circulation* 1994; 90: 1-24.
- 40 Jordan C, Carvalho H, Fajadet J, Bernard C, Robert G, Marco J. Reduction of subacute thrombosis rate after coronary stenting using a new anticoagulant protocol. *Circulation* 1994; 90: 1-25.
- 41 Yoshioka T, Mirich D, Wright KC, Wallace S. Self-expanding endovascular graft: an experimental study in dogs. *Am J Radiol* 1988; 15: 673-676.
- 42 Roeren T, Garcia OJ, Palmaz JC, Rees CR, Tio FO. Intraarterial compatibility of a balloon-expandable tubular graft. *Radiology* 1990; 174: 1069.
- 43 De Scheerder IK, Wilczek KF, Verbeke E et al. Amphiphilic polyurethane coating of intracoronary stents decreases mortality due to subacute thrombosis in a porcine coronary model. *J Am Coll Cardiol* 1994; 23: 186A.
- 44 Sheth S, Park KD, Dev V et al. Prevention of stent subacute thrombosis by segmented polyurethane-polyethylene oxide-heparin coating in the rabbit carotid. *Am J Coll Cardiol* 1994; 23: 187A.
- 45 Schwartz RS, Huber KC, Edwards WD et al. Native fibrin film as a biocompatible, absorbable material for intracoronary stent implant and drug delivery. *J Am Coll Cardiol* 1992; 19: 171A.
- 46 de Jaegere PPT. Endovascular stents: preliminary clinical results and future developments. *Clin Cardiol* 1993; 16: 369-378.
- 47 Lincoff AM, Furst JG, Ellis SC, Topol EJ. Sustained local drug delivery by a novel intravascular eluting stent to prevent restenosis in the porcine coronary artery. *J Am Coll Cardiol* 1994; 23: 18A.
- 48 Eigler NL, Lambert TL, Dev V et al. Local arterial wall drug delivery from a polymer coated removable metallic stent: kinetics, distribution and bioactivity of forskolin. *J Am Coll Cardiol* 1994; 23: 4A.
- 49 Hastings GW, ed. *Cardiovascular Biomaterials*. London: Springer-Verlag; 1992.
- 50 Murphy JG, Schwartz RS, Huber KC, Holmes DR. Polymeric stents: modern alchemy or the future? *J Invasive Cardiol* 1991; 3: 144-148.
- 51 Szycher M, Lee SJ. Cardiovascular device for the 1990s. *J Biomater Appl* 1993; 8: 31-63.
- 52 Devanathan TD. Silicone elastomers for implantable biomedical devices. In: Szycher M, ed. *Biocompatible Polymers, Metals and Composites*. Technomic Publishing Co. Inc., 1983: 769.
- 53 Hinrichs WLJ, Zweep HP, Satoh S, Feijen J, Wildevaar ChRH. Supporting microsporous elastomeric, degradable prostheses to improve the arterialization of autologous vein grafts. *Biomaterials* 1994; 15: 83-91.
- 54 Porter J, Ahsan A, Mulcahy D, Sigwart U. Coronary stents. *Br J Hosp Med* 1992; 47: 411-419.
- 55 Murphy JG, Schwartz RS, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Percutaneous polymeric stents in porcine coronary arteries: initial experience with polyethylene terephthalate stents. *Circulation* 1992; 86: 1596-1604.
- 56 Harasaki H, Kiraly RJ, Nose Y. Blood-blood pump surface interaction. In: Szycher M, ed. *Biocompatible Polymers, Metals and Composites*. Technomic Publishing Co. Inc., 1993: 208.
- 57 Schwartz RS, Huber KL, Murphy JG et al. Restenosis and the proportional neointimal response to coronary artery. *J Am Coll Cardiol* 1992; 19: 267-274.
- 58 Mitchell JF, Azrin MA, Fram DB et al. Intramural deposition of urokinase at the angioplasty site—Comparative efficiency of systemic and local drug delivery techniques. *Circulation* 1994; 90: 1-20.
- 59 Thomas CN, Robinson KA, Cipolla GD, Jones M, King SB, Scott NA. *In vivo* local delivery of heparin to coronary arteries with a microsporous infusion catheter. *J Am Coll Cardiol* 1994; 23: 187A.
- 60 Thomas CN, Barry JJ, King SB, Scott NA. Local delivery of Heparin with a PTCT infusion balloon inhibits platelet-dependent thrombosis. *J Am Coll Cardiol* 1994; 23: 4A.
- 61 Jenkins GM, Leong K, Heller P et al. Local delivery of taxol inhibits neointimal regrowth following balloon injury of the rat carotid artery. *Circulation* 1994; 90: 1-297.
- 62 Meyer B, Fernandez-Ortiz F, Fuster V et al. Local delivery of γ -hirudin by a double balloon perfusion catheter inhibits platelet deposition post angioplasty. *J Am Coll Cardiol* 1994; 23: 18A.
- 63 Slepian MJ, Massia SP. Local delivery of a YIGSR peptide inhibits neointimal hyperplasia following balloon injury. *Circulation* 1994; 90: 1-297.
- 64 Rfng EJ, Schwarz W, McLean GK, Freiman A. A simple, indwelling, biliary endoprosthesis made from commonly available catheter material. *Am J Radiol* 1982; 139: 615-619.
- 65 Davids PHP, Groen AK, Rauws EAJ, Tytgat GNJ, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; 340: 1488-1492.
- 66 Shaper NJ, Rutt DR, Browse NL. Use of Teflon stents for lymphovenous anastomosis. *Br J Surg* 1992; 79: 633-636.
- 67 Kempainen E, Taija M, Riihela M, Pohjonen T, Tormala P, Alifhan O. A bioresorbable urethral stent. *Urol Res* 1993; 21: 235-238.
- 68 Goldberg JR. Biodegradable stents. *European Patent 0420541 A2*.
- 69 Rothman M, Davies SW. *Br Heart J* 1992; 67: 425-427.
- 70 Duprat G, Wright KC, Charnsangavej C, Wallace S, Gianturco C. Self-expanding metallic stents for small vessels: an experimental evaluation. *Radiology* 1987; 162: 469-472.
- 71 Murphy JG, Schwartz RS, Kennedy K et al. A new biocompatible polymeric coronary stent: design and early results in a pig model. *J Am Coll Cardiol* 1990; 15: 105A.
- 72 Murphy JG, Schwartz RS, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Experimental coronary artery stenosis induced by polymer (PET) implantation in domestic swine. *J Am Coll Cardiol* 1991; 17: 195B.
- 73 van der Giessen WJ, Slager CJ, Gussenhoven EJ et al. Mechanical features and *in vivo* imaging of a polymer stent. *Intern J Cardiac Imaging* 1993; 9: 219-226.
- 74 van der Giessen WJ, Slager CJ, van Busekom HMM et al. Mechanical features and *in vivo* behaviour of a polymer stent. *J Am Coll Cardiol* 1992; 19: 49A.
- 75 Zhang XC. Biodegradable lactide polymers: synthesis, degradation and drug controlled release properties. PhD thesis. Kingston, Canada: Queen's University, 1993.
- 76 Agrawal CM, Clark HG. Deformation characteristics of a bioabsorbable intravascular stent. *Invest Radiol* 1992; 27: 1020-1024.
- 77 Chapman GD, Gammon RS, Bauman RP et al. A bioabsorbable stent: initial experimental results. *Circulation* 1990; 82: III-72.

- 78 Beck A. Über eine neue ballonexpandierbare kunststoffendoprothese: erster erfahrungsbericht über den modellierbaren thermostent. *Radiologe* 1990; 30: 347-350.
- 79 Eury RP. Multilayered biodegradable stent and method for its manufacture. *European Patent 604022 A1*.
- 80 Lincoff AM, Schwartz RS, van der Giessen WJ et al. Biodegradable polymer can evoke a unique inflammatory response when implanted in the coronary artery. *Circulation* 1992; 86: 1-801.
- 81 in't Veld PJ, Dijkstra PJ, Feijen J. Synthesis of biodegradable polyesteramides with pendant functional groups. *Makromol Chem* 1992; 193: 2713-2730.
- 82 Barrera DA, Iylstra E, Lansbury PT, Langer R. Synthesis and RGD peptide modification of a new biodegradable copolymer: poly(lactic acid-co-lysine). *J Am Chem Soc* 1993; 115: 11010-11011.
- 83 Hrkach JS, Ou J, Langer R. The development of poly(L-lactic acid-co-L-lysine) for tissue engineering: functionalization and new monomer synthesis. *Polym Preprint* 1994; 35(2): 450-451.
- 84 Slepian MJ, Massia SP. Local delivery of a cyclic RGD peptide inhibits neointimal hyperplasia following balloon injury. *Circulation* 1993; 88: 1-372.
- 85 Minra Y. Antithrombogenic biomedical materials improved by enzyme immobilization technique. In: Szycher M, ed. *Biocompatible Polymers, Metals, and Composites*. Technomic Publishing Co. Inc., 1983: 301.
- 86 Slepian MJ, Schindler A. Polymeric endoluminal paving/sealing: a biodegradable alternative to intracoronary stenting. *Circulation* 1988; 78: II-409.
- 87 West HJL, Chowdhury SM, Slepian MJ, Hubbell JA. The hydrogel barriers for prevention of thrombosis and intimal thickening after balloon injury. *J Am Coll Cardiol* 1994; 24: 5A.
- 88 Slepian MJ, Campbell PK, Berrigan K et al. Biodegradable endoluminal polymer layers provide sustained transmural heparin delivery to the arterial wall *in vivo*. *Circulation* 1994; 90: 1-20.
- 89 Hill West JL, Chowdhury SM, Slepian MJ, Hubbell JA. Resorbable hydrogel barriers for controlling intravascular thrombosis and healing. *Polym Preprint* 1994; 35(2): 396-398.
- 90 Slepian MJ, Massia SP, Sawhney A. Endoluminal gel paving using *in situ* biodegradable photopolymerized hydrogel: acute efficacy in the rabbit. *Circulation* 1993; 88: 1-660.



Recon
facial
almo:
restit
espec
predc
howe
predc
the d
probl
limite
newt
postc
alterr
demi
been
exam
disad
biolo
Corre: